

Serum Zinc and Copper Level in Juvenile Idiopathic Arthritis (JIA) Patients and Its Correlation with Disease Duration-A Tertiary Hospital Study

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Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is the most prevalent rheumatic disease in children. It is associated with abnormal levels of serum zinc (Zn) and copper (Cu) as during inflammation serum copper concentration increases and zinc decreases. **Objective:** To assess the serum Zn and Cu levels in different sub-types of JIA patients and their correlation with the disease duration. **Methods:** This cross-sectional study was conducted over twelve months at the Pediatric Rheumatology Division, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University. Sixty-nine JIA cases that fulfilled the International League of Association for Rheumatology (ILAR) criteria were taken as cases and age and sex-matched healthy children were considered as controls. The serum Zn and Cu tests were done using the spectrophotometric method with INDIKO PLUS Drug Analyzer. Data were recorded in a pre-designed questionnaire. Data were checked, verified and analyzed manually where continuous variables were analyzed using unpaired t-test and categorical variables using the ANOVA test. Pearson's correlation coefficient test was used to see the correlation of serum zinc and copper levels with disease duration. **Results:** Boys were predominant in both case and control groups, with the majority within the 10 to 16-year-age group. Enthesitis-related arthritis (ERA) was the most common subtype followed by sJIA, Oligo JIA, Poly JIA (RF-) and unclassified subtypes. Disease duration was found less than 12 months in 30.4% of JIA patients. Serum analysis revealed a statistically significant reduction in mean zinc levels and increased copper levels in JIA patients compared to controls. This study observed a negative correlation between

serum zinc levels and disease duration, whereas serum copper levels exhibited a positive correlation with disease duration. **Conclusion:** In conclusion, this study revealed that JIA patients exhibit alterations in serum zinc and copper levels. Serum copper levels showed a positive correlation and serum zinc levels showed a negative correlation with the duration of the disease.

Keywords

Copper, Juvenile Idiopathic Arthritis, Zinc

1. Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease and one of the most common chronic illnesses of childhood [1]. JIA is defined by the International League of Associations for Rheumatology (ILAR) as arthritis of unknown etiology beginning before the sixteenth birthday and persisting for at least six weeks with other known conditions excluded [2]. JIA is an important cause of short and long term disability [3] [4]. JIA is classified into seven subgroups according to ILAR 2001 classification criteria [5]. The etiology and pathogenesis of JIA are not completely understood, although both immunogenetic susceptibility and external triggers are considered. Alterations in both humoral and cell-mediated immunity and T lymphocyte play a central role. Releasing cytokines and favoring a type 1 helper T lymphocyte response are observed in the JIA pathogenesis [6] [7].

Copper and zinc are essential nutrients; they are constituents of the superoxide-dismutase enzyme which has intracellular antioxidant functions [8]. Trace elements such as zinc (Zn) and copper (Cu) are crucial catalytic cofactors for several enzymes, structural proteins, and transcription factors. In addition, they are essential elements for the immune system, and the integrity of the articular tissues [9] [10]. Furthermore, Cu is a constituent of ceruloplasmin, a powerful extracellular antioxidant enzyme. It is also the constitution of enzymes that transfer electrons (oxidases) and is therefore essential for energy metabolism at the cellular level. Among them, lysyl oxidase is an enzyme that plays a crucial role in the formation of connective tissues. It utilizes lysine and hydroxylysine, which are components present in collagen and elastin, as substrates.

This enzyme is responsible for creating the essential cross-links that contribute to connective tissues' structural integrity and development, including those in bones [11]. Moreover, Zn constitutes a structural element of alkaline phosphatase and stimulates its synthesis in osteoblasts, playing an important role in bone mineralization [12].

The anti-inflammatory effects of Cu and Zn have been documented in humans. Meanwhile, acute or chronic inflammation induces metabolism alterations of these minerals, which are reflected in their serum and tissue levels [13]. Önal *et al.* in their study found that the copper level was significantly higher and

zinc was lower in JIA patients relative to controls [14]. Talaat *et al.* concluded that the alteration of serum copper and zinc probably is a defense response against JIA and increased copper may be due to inflammation [15] [16]. Among Bangladeshi JIA patients, there was no such study related to Zn and Cu estimation in this cohort. Herein, we reported the serum levels of Zn and Cu in different sub-types of JIA patients and their correlation with the disease duration in this study.

2. Methods

This cross-sectional study was carried out in the Paediatric Rheumatology division, Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) among Bangladeshi children across different part of country from January, 2022 to December, 2022. Sixty-nine diagnosed cases of different sub-types of JIA fulfilling ILAR (International League against Rheumatism) criteria were included in this study. Thirty age and sex-matched healthy controls were selected for comparison with cases. JIA patients with acute infection, chronic liver disease, renal failure, malignancy and patients got supplementation of zinc in last one month were not included in this study as abnormal level of zinc and copper might be found. History, clinical examination and relevant investigations were recorded in the predesigned questionnaire.

After taking informed written consent blood samples were collected for CBC, erythrocyte sedimentation rate (ESR), serum creatinine, serum ALT, serum zinc, serum copper level, and urine analysis. The serum Zn and Cu analysis were done at the Department of Biochemistry, BSMMU by Spectrophotometric method with INDIKO PLUS Drug Analyzer. This study was conducted with prior approval of the Institutional Review Board of BSMMU, Dhaka, Bangladesh. (NO: BSMMU/2020/9954) Data were checked, verified and analyzed manually. Continuous variables were analyzed using unpaired t-test and categorical variables using ANOVA test. Pearson's correlation coefficient test was used to see the correlation of serum zinc and copper level with disease duration. A p-value less than 0.05 was considered as significant.

3. Results

Demographic characteristics of the study samples were shown in **Table 1**. Majority of the study samples were found male both in the case and control group. Almost half of the case and control were found within 10 to 16 years of age group were observed in the both groups. Disease duration was found less than 12 months among 30.4% of JIA patients.

Among the sub-types of JIA, Enthesitis Related Arthritis (ERA) was the majority (36.2%) subtype followed by sJIA (30.4%), Oligo JIA, Poly JIA RF- and unclassified subtypes (**Table 2**).

Mean serum zinc level was reduced and serum copper level was raised in JIA patients compared to control observed in this study which was statistically significant (**Table 3**).

Table 1. Baseline demographic characteristics of case and control of study population.

Characteristics	Case (n = 69)		Control (n = 30)	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Age				
<5 years	6	8.7	3	10
5 - 10 years	27	39.1	13	43.33
>10 - 16 years	36	52.2	14	46.66
Gender				
Male	39	56.5	18	60
Female	30	43.5	12	40
Age at disease onset (years) (mean \pm SD)	7.66 \pm 3.70			
Disease duration (months)				
<12	21	30.4		
12 - 18	11	15.9		
>18 - 24	11	15.9		
>24 - 36	6	8.7		
>36 - 48	20	29.0		
Mean \pm SD	23.2 \pm 14.4			

Table 2. Sub types of JIA cases (n = 69)

Variables	Frequency	Percentage
ERA	25	36.2
sJIA	21	30.4
Poly JIA RF+	6	8.7
Poly JIA RF-	8	11.6
Oligo JIA	8	11.6
Unclassified	1	1.4

Table 3. Comparison of serum zinc and copper level between the JIA patients and the control group.

Variables	Cases (n = 69)	Control (n = 69)	P value
	Mean \pm SD	Mean \pm SD	
Zinc (mcg/dl)	84.6 \pm 39.8	101.4 \pm 25.3	0.036*
Copper (mcg/dl)	121.9 \pm 42.83	88.6 \pm 8.9	<0.001*

p-value obtained by Unpaired t-test, *significant.

Comparison of mean level of serum zinc and copper in ERA, SJIA, Oligo JIA and Poly JIA patients were not statistically significant (**Table 4**).

In **Figure 1** shows serum zinc level was negatively correlated with disease duration of JIA patients. In **Figure 2** shows serum copper level was positively

Table 4. Comparison of serum zinc and copper with subtypes of JIA.

Variables	ERA	sJIA	Oilgo JIA	Poly JIA	<i>p</i> -value
	(n = 25)	(n = 21)	(n = 8)	(n = 14)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Zinc (mcg/dl)	109.88 ± 64.06	89.36 ± 39.79	82.58 ± 34.33	74.38 ± 32.72	0.182 ^{ns}
Copper (mcg/dl)	110.24 ± 51.69	125.55 ± 32.56	125.21 ± 34.74	120.02 ± 54.98	0.834 ^{ns}

p-value obtained by ANOVA test, ns = not significant.

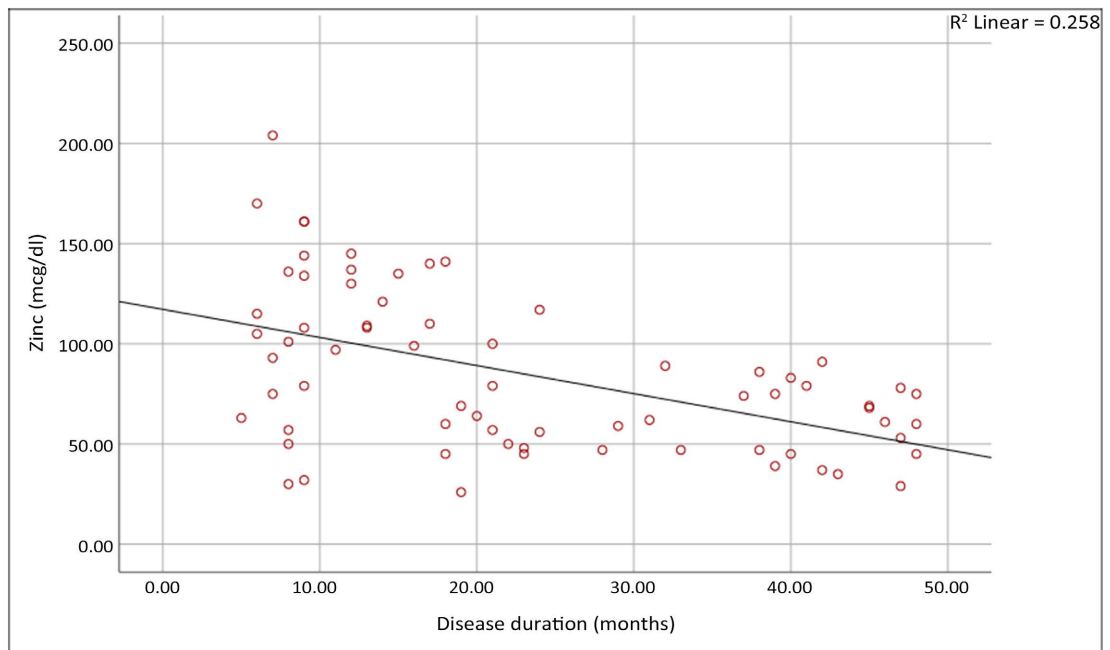


Figure 1. Correlations between levels of serum zinc with disease duration of JIA patients ($r = -0.507$, $p < 0.001$).

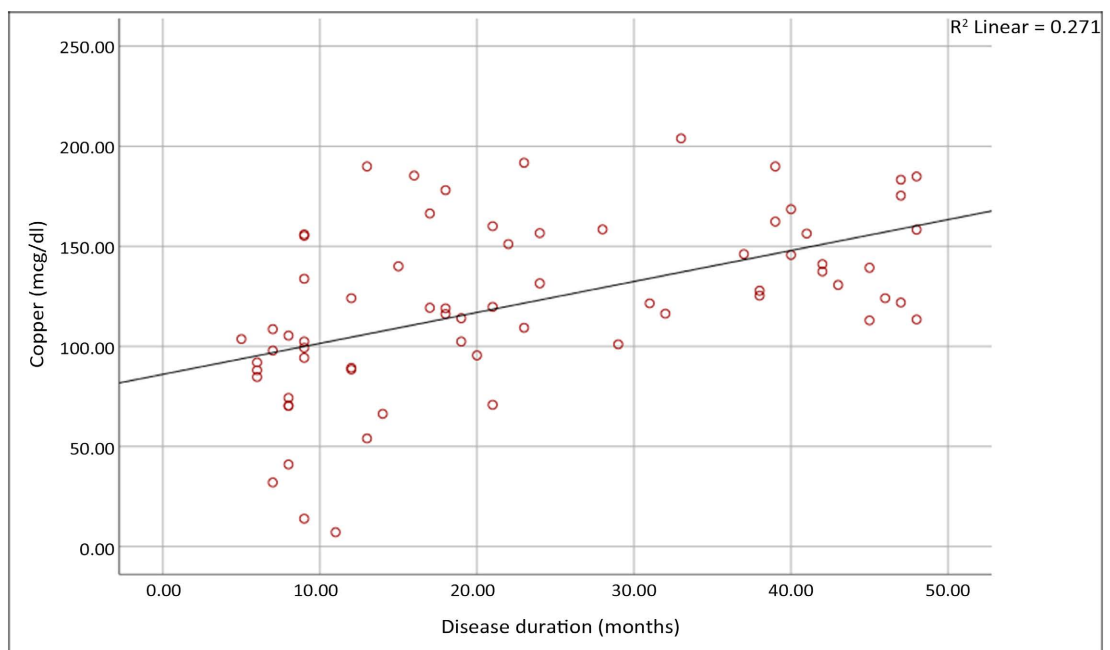


Figure 2. Correlations between levels of copper with disease duration of JIA patients ($r = 0.521$, $p < 0.001$).

correlated with disease duration of JIA patients.

4. Discussion

Juvenile Idiopathic Arthritis (JIA) is the most common chronic arthropathy in childhood which is a leading cause of short and long-term disability [17]. The importance of trace elements e.g., zinc and copper in chronic inflammatory arthritis is related to their role in different metabolic processes in articular tissues and in the functions of the immune system [9] [10]. For that reason, determination of serum levels of these trace elements may help to identify joint involvement in the JIA patients.

The mean age of JIA patients was 7.66 ± 3.70 years in this study which corresponds to another Bangladeshi study done by Islam MI *et al.*, where the mean age was 8.33 ± 4.8 years [18]. But in the Moroccan study by Bouaddi *et al.* where mean age was 11 years, which can explain the juvenile onset of the disease in most of the contexts [19]. Also in this study, more than 10 years of age group were observed in majority of the both cases (52.2%) and control (46.6%), which was similar to another study held in our institute done by Rahman *et al.*, where they found most (45.5%) of the JIA patients age group were 11 - 16 years [20].

In the present study, disease duration was found less than 12 months in most cases (30.4%) of JIA patients. In the other studies held in this center, disease duration was found more than 1 year in most cases [20]. This is due to the increasing trend of awareness of JIA among people of this country.

A Bangladeshi study by Rahman *et al.* showed that the male-female ratio was 2:1 where 68% were male and 32% were female, which was relevant to this study, where samples were found male predominant both in the case and control group, male-female ratio was 1.5:1 [20]. But in Egyptian study by Talaat *et al.* found male to female ratio of 1:1.5 [16]. Increased numbers of female patients can be due to the more chance of autoimmune disease in females. Studies showed male predominance in this subcontinent, may be due to our socio-cultural background, where parents provide more emphasize to their male child and brought to the hospitals early and frequently.

In the present study, six sub-types of JIA patients were found. Among them, Enthesitis related arthritis (ERA) was the majority (36.2%) subtypes followed by sJIA (30.4%), Oligo JIA, Poly JIA RF-ve, poly JIA RF +ve and unclassified subtypes which corresponds to another Bangladeshi study by Sonia SP *et al.*, Indian study by Kunjir *et al.* and a study from Taiwan region by Shen *et al.* where ERA was the most common subtype [18] [21] [22]. The reason for the high frequency of ERA in these studies might be male predominance, early health-seeking attitude for boys and increased frequency of this variety in the Asian subcontinent.

Mean serum Zinc level were reduced (84.6 ± 39.8) in this study in comparison with control (101.4 ± 25.3) but which was not statistically significant, and serum copper level were raised (121.9 ± 42.83) than control (88.6 ± 8.9) in JIA patients which was statistically significant.

Both in an Egyptian study by Yasser *et al.* and Brazilian study by OM Silverio Amancio *et al.* results correspond with the present study results where they found the mean serum Cu level was highly statistically significantly higher in the JIA patients' group than in the control group and the mean serum Zn level was lower in the JIA patients compared to the control group but it was not significant [8] [23].

Mean level of serum Zinc and Copper level in different sub-types of JIA patients were not significantly related in our study. Contrary to this study, Yasser *et al.* found the mean serum Cu concentration was lower in oligoarticular JIA patients than in polyarticular JIA patients and the mean serum Zn concentration was higher in oligo JIA patients than in poly JIA patients [23].

In the present study, serum zinc level was negatively and serum copper level was positively correlated with the disease duration of JIA patients. Contrary to this study, Yasser *et al.* found insignificant correlations between serum Cu concentrations and the disease duration and between serum Zn concentrations and the disease duration [23].

5. Conclusion

It may be concluded that serum Zinc level was reduced and serum copper level was found raised in JIA patients compared to control in this study. There was a negative correlation between the serum zinc level and disease duration, while the serum copper level showed a positive correlation with the disease duration in JIA patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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